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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/782,383	02/19/2004	Katsuro Tachibana	EKOS.8CP3DV1C4	3583

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EXAMINER	
SCHNIZER, RICHARD A	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 10/19/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/782,383	TACHIBANA ET AL.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 August 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-6,9-12 and 14-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-6,9-12 and 14-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/158,316.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/29/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

An amendment was filed 8/29/06.

Claims 2, 3, 7, 8, and 13 were canceled.

Claims 1, 4-6, 9-12, and 14-27 remain pending and are under consideration in this Office Action.

Previous rejections not reiterated in this Action are withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4-6, 9-12, and 15-27 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to methods of delivering a therapeutic composition to a target site comprising "delivering a therapeutic composition comprising an oligonucleotide covalently attached to a light activated drug through a catheter to the target site". It is unclear from the claims as written if the recited oligonucleotide is intended to be therapeutic. However, a review of the specification shows that oligonucleotide is intended to be delivered for the purpose of therapy (see e.g.

paragraph 2 at page 1; paragraph 131-133 at pages 20 and 21), and in fact, no other purpose for delivering an oligonucleotide is disclosed. For that reason, the claims are interpreted as therapeutic methods, and the oligonucleotide is interpreted as intended in the specification, i.e. as a therapeutic. As a result, the claims are considered to be drawn broadly to methods of oligonucleotide therapy. The claims do not limit the identity of the oligonucleotide to be delivered, or the nature of the therapeutic effect that is intended.

At the time the invention was made, successful implementation of gene therapy protocols was not routinely obtainable by those skilled in the art. This is reflected by three recently published reviews. Orkin (Report and Recommendations of the Panel to Assess the NIH Investment in Research on Gene Therapy, 1995) taught that "significant problems remain in all basic aspects of gene therapy. Major difficulties at the basic level include shortcomings in all current transfer vectors and an inadequate understanding of the biological interaction of these vectors with the host" (page 1, item 3). Orkin taught that problems exist in delivering nucleic acid sequences to the appropriate target cell or tissue and achieving the appropriate level of expression within that cell or tissue (page 9). Verma et al (Nature 389: 239-242, 1997) taught that "there is still no single outcome that we can point to as a success story (p. 239, col 1). The authors stated further, "Thus far, the problem has been the inability to deliver genes efficiently and to obtain sustained expression" (p.239, col. 3). Anderson (Nature 392:25-30, 1998) confirmed the unpredictable state of the art, stating that "there is still no conclusive evidence that a gene-therapy protocol has been successful in the

treatment of human disease" (p. 25, col. 1) and concluding, "Several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered" (p.30). More recently, Romano et al (Stem Cells 18:19-39, 2000) reviewed the general state of gene therapy, and found that the problems relating to gene delivery and expression discussed above persisted. See entire document, especially, last sentence of abstract; last sentence of column 1 on page 20 to column 2, line 6; page 21, column 1, lines 1-9 and 18-21; sentence bridging columns 1 and 2 on page 21; and first sentence of last paragraph on page 21. This idea was echoed by Somia and Verma (Nature Reviews/Genetics 1: 9199, 11/2000), who noted that delivery vehicles still represented the Achilles heel of gene therapy, and that no single vector existed that had all of the attributes of an ideal gene therapy vector. See page 91, column 1, lines 5-13 of first paragraph.

The state of the art with respect to oligonucleotide-based therapies indicates a high level of unpredictability. Crooke (In Basic Principles of Antisense Therapeutics, Springer-Verlag, Eds, New York, pgs. 1 and 4), taught that although antisense oligonucleotide techniques have progressed rapidly, "the technology remains in its infancy", and the utility of the approach is still debatable (pg. 1, Introduction). Crooke pointed out several factors that may influence the biological effect of an antisense oligonucleotide (AODN), including the rate of uptake of the AODN, rate of distribution within the target cell, stability within the target cell, local concentration of the oligonucleotide, and the concentration and stability of the target mRNA (pgs. 1 and 4). Furthermore, Branch (Trends in Biochem. Sci 23: 45-50, 1998) taught that selection of

appropriate antisense sequences is difficult because secondary structures of mRNAs *in vivo* frequently restrict access of antisense oligonucleotides to the target sequence (page 45, col. 3. first para., page 48, last para. and page 49). Branch stated, "Since accessibility cannot be predicted, rational design of antisense molecules is not possible" (page 49, col. 2, last para.). Ho and Parkinson (Sem. Drug Discov. 24(2): 187-202, 1997) taught that although antisense therapy is simple in theory, it "has proven to be much more complex in practice. A number of important challenges in the preclinical development of antisense oligonucleotides have been identified, including stability, sequence length, cellular uptake, target sequence selection, appropriate negative controls, oligonucleotide:protein interactions, and cost of manufacture." The authors concluded that "[c]ontinued progress in this arena will require that many of the preclinical challenges confronting antisense development are satisfactorily resolved." See abstract. Akhtar (J. Antimicrob. Chemother. 38(2): 159-165, 1996) taught that "a healthy degree of concern exists among scientists and administrators as to whether antisense and, to some extent, ribozyme oligonucleotides will ever become useful therapeutic agents." See page 163, column 1, lines 5-14 of first full paragraph. Thus, at the time the invention was made, there was considerable unpredictability in the design of antisense oligonucleotides, their delivery and pharmacodynamics, and most importantly, whether or not they would ultimately have any therapeutic value.

Guidance in the specification regarding oligonucleotide therapy is insufficient in view of the state of the art. The specification indicates at the paragraph bridging pages 14 and 15 that oligonucleotides can be used target specific DNA sites in a cell for

cleavage by activation of the light activatable drug. For example, the "light activated conjugate can be targeted to a site on viral DNA where activation of the light activated conjugate causes the virus to be killed. Similarly, the light activated conjugate can be targeted to oncogenes." However, a search of the prior art did not reveal any therapeutic use of oligonucleotide directed nucleic acid-cleaving drugs, so it appears that further guidance in the specification as to such use is required. Other therapeutic applications of targeted DNA cleavage include antisense applications and chemotherapy. The specification provides no specific guidance at all regarding the use of the invention in chemotherapy. Regarding antisense therapy, antisense oligonucleotides against Ras and IL-2 are envisioned at paragraphs 132 and 134 on page 21. No other specific oligonucleotides are disclosed for any therapeutic purpose, and no specific therapeutic purpose is envisioned for the use of anti-Ras or anti-IL-2 oligonucleotides. Instead one of skill in the art is left to develop therapeutic oligonucleotides for their own purposes. However, the state of the art as discussed above was such that oligonucleotide-mediated therapies were not routine at the time of the invention. As a result some guidance in the specification is required. Such guidance is essentially limited to means of delivering oligonucleotide conjugates to a specific tissue site. However, as discussed above, Crooke taught that there were a number of intracellular issues to be considered in oligonucleotide therapeutics including rate of uptake of the oligonucleotide, rate of distribution within the target cell, stability within the target cell, local concentration of the oligonucleotide, and the concentration and stability of the target mRNA.

The specification provides no working example of any method of oligonucleotide-mediated therapy, or even of delivery of an oligonucleotide in vivo or in vitro. No guidance is provided as to the particular site to which any oligonucleotide therapeutic must be delivered for any therapeutic purpose, nor to the selection of any oligonucleotide for any therapeutic purpose. No guidance is provided as to how to obtain and maintain therapeutic levels of oligonucleotides.

In view of the state of the art at the time of the invention (8/5/98) as discussed above, the level of unpredictability in the art particularly with regard to oligonucleotide delivery and pharmacokinetics, and the limited guidance and lack of working examples in the specification, and the broad scope of oligonucleotides and therapies embraced by the claims, one of skill in the art could not have practiced therapeutic oligonucleotide delivery as broadly claimed without undue experimentation.

Response to Arguments

Applicant's arguments filed 8/29/06 have been fully considered but they are not persuasive.

Applicant argues at page 7 of the response that the claims, as amended to be limited to oligonucleotides, overcome the rejection because they avoid the problems outlined in the rejection, particularly because the claims require delivery to a target site. This is unpersuasive for the reasons set forth in the rejection, i.e. the state of the art at the time of the invention was such that oligonucleotide-mediated therapies were not routine due to a variety of unpredictable intracellular factors such as rate of uptake of the AODN, rate of distribution within the target cell, stability within the target cell, local

concentration of the oligonucleotide, the concentration and stability of the target, and oligonucleotide:protein interactions. The specification does not provide any guidance as to what specific oligonucleotides can be used for any specific therapeutic purpose, although the scope of therapeutic outcomes embraced is broad. For these reasons the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 14 is rejected under 35 U.S.C. 103(a) as being unpatentable over any one of Berg et al (US 6,680,301), Berg et al (US 5,876,989), or Berg et al (WO 96/07432), any one taken with Craig et al (US Patent 5,766,902).

The '989 patent is the national phase of the '432 publication, and is considered to disclose the same subject matter.

The Berg patents taught that molecules of interest such as oligonucleotides could be delivered to cells by photochemical internalization by means of contacting cells with a photoactivatable drug and the oligonucleotide. Berg also taught that the photoactivatable drug could be conjugated to the molecule of interest. See the '301 patent at column 2, lines 61-64; the '989 patent at column 2, lines 24-36, and claim 2; or the '432 publication at the paragraph bridging pages 2 and 3, and at claims 9 and 12.

The Berg references do not specify that the conjugation should be covalent, however, one of ordinary skill in the art is aware of that compounds may be conjugated by any of a variety of covalent or ionic means, and that these means can be considered to be equivalent, or a matter of design choice. As evidence of this see Craig who taught that nucleic acids, ligands, and polycations may be conjugated to each other by covalent, ionic or hydrogen bonds. See column 8, lines 14-23. As a result it would have been obvious to one of ordinary skill in the art at the time of the invention to use covalent means to conjugate the photoactivatable drug and the oligonucleotide either directly or through an intermediate carrier, as taught by any of the Berg references.

Thus the invention as a whole was prima facie obvious.

Response to Arguments

Applicant's arguments filed 8/29/06 have been fully considered as they might apply to the ground of rejection set forth above, but they are not persuasive.

Applicant argues that the amendment to require covalent bonding of the light activated drug and the nucleic acid overcomes the obviousness rejection. This is unpersuasive because it would have been obvious to use a covalent conjugation in any of the publications of Berg, as evidenced by Craig. See above. Applicant argues that the Examiner has not pointed to any therapeutic compound. This is unpersuasive first because the claim does not require any therapeutic compound, and second because the photoactivatable drug can be considered to be a therapeutic compound. For these reasons the rejection is considered to be proper.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Peter Paras, can be reached at (571) 272-4517. The official central fax

number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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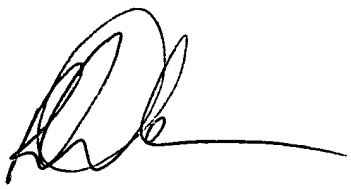

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Art Unit 1635